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INJECTABLE STEROID COMPOSITIONS CONTAINING AT LEAST 75% BENZYL BENZOATE

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This invention relates to compositions of matter and more particularly to new parenterally administrable pharmaceutical compositions comprising one or more active medicaments and a physiologically acceptable non-toxic pharmaceutical vehicle, comprised essentially of benzyl benzoate.

The active medicament which may be incorporated in the novel compositions of this invention may be any one which is administered for use in comparatively large unit dosages, for example, 10 mg./ml. to 500 mg./ml. and which is soluble in benzyl benzoate. Examples of the medicaments which may be employed in this invention include inter alia, steroid hormones, especially those steroid hormones which exhibit anabolic, estrogenic, androgenic and progestational activity, for example, 17-hydroxyprogesterone and the esters thereof, testosterone, estradiol and the acid esters thereof, progesterone and its derivatives and Δ^1-testololactone and its derivatives. In the most preferable embodiment of this invention the active medicament is a steroid hormone although other pharmaceutically active compounds may also be employed, with satisfactory results.

Heretofore it has been well recognized in the preparation of parenterally administrable pharmaceutical compositions that a suitable solvent must be employed to render the composition injectable. However, as the science of medicine has progressed it has been found that increasingly higher dosages of certain medicaments must be employed in the treatment of certain ailments in order to achieve several advantages. Among these advantages can be numbered the prolongation of activity of the medicaments involved and the lessening of the total number of individual injections which are needed to obtain the same results.

Additionally, it has been found that new chemical modifications of medicaments are continually being discovered and the solubility of these modified medicaments in the solvents commonly employed, appears to be more and more limited and it has therefore become increasingly difficult to dissolve these new modified medicaments in parenterally acceptable vehicles. It is well-known that certain pharmaceutical vehicles yield satisfactory results at low level medicament concentrations when employed in compositions for parenteral administration. Such vehicles are the vegetable oils such as cotton seed oil, peanut oil, sesame oil, or corn oil, in combination with small amounts of benzyl benzoate. However, when an increased dosage level of the medicaments is employed, along with a correspondingly necessary increased amount of pharmaceutical vehicle it has been found that certain undesirable disadvantages exist.

The undesirable disadvantages which are present when the prior art vehicles are employed with a high dosage level of medicaments, are many. In addition to the prior art vehicles being incapable of solubilizing any great quantities of the medicaments, it has been found that the compositions heretofore employed produce an undue amount of irritation at the site of injection, when parenterally administered into the animal being treated.

It has now been found that the disadvantages encountered in the parenteral administration of high dosage levels of the medicaments of this invention can be avoided by employing the novel pharmaceutical compositions of

this invention. It has been found that these disadvantages can be overcome by employing benzyl benzoate as the essential component of the pharmaceutical vehicle of parenterally administrable compositions. The benzyl benzoate has been found to be capable of dissolving great quantities of the medicaments of this invention and the resulting parenterally administrable composition employing this vehicle does not produce undue irritation when injected into the animals being treated.

The amount of benzyl benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed. Thus the ratio of benzyl benzoate present in the pharmaceutical vehicle as compared to any other ingredients therein must be at least 3 to 1. In the most preferable embodiment of this invention it has been found that a pharmaceutical vehicle consisting essentially of pure benzyl benzoate yields the best results although at lower levels satisfactory results are also obtained.

As is common in the art of preparing parenterally administrable pharmaceutical compositions other additives such as preservatives, antioxidants or anesthetics, such as benzyl alcohol and the other like well known additives may also be included in the pharmaceutical compositions of this invention. However, their use herein is permissive and not mandatory as their incorporation or omission in the final product of this invention does not substantially affect the results herein obtained.

The compositions of this invention are easily prepared by merely taking the desired amount of medicament and dissolving it in the pharmaceutical vehicle of this invention by any means known in the art, for example, by mere stirring.

The final compositions of this invention are parenterally administrable to the animal being treated. The administration of the composition may be accomplished intramuscularly, subcutaneously or in any other manner known to the art as may be determined in the individual cases wherein this invention is employed. It has been generally found that the most preferable results are obtained when an intramuscular route of administration is employed, although other methods of administration will also give satisfactory results.

The invention is more particularly illustrated by the following examples:

Example 1

Two g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 10 ml. of benzyl benzoate with stirring and warming. The resultant solution is then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for two hours.

0.25 ml. of the resulting solution is then injected into the vastus lateralis muscle of a rabbit producing a lesion at the site of the injection having the size of about 640 cubic millimeters after two days.

When 2 g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 4.5 ml. of benzyl benzoate and 5.5 ml. of castor oil in accordance with the procedure of Example 1 and 0.25 ml. of the resultant solution is injected intramuscularly into the rabbit a lesion at the site of injection having a size of 967 cubic millimeters after two days.

Example 2

The procedure of Example 1 is followed except that 2 g. of testosterone palmitate are substituted for the acetophenone derivative of 16,17-dihydroxyprogesterone of Example 1.

0.25 ml. of the resultant solution is injected intramus-

cularly into a rabbit producing a lesion at the site of injection having the size of about 420 cubic millimeters after two days. When 2 g. of testosterone palmitate are dissolved in a vehicle consisting of 40% castor oil and 60% benzyl benzoate and the resultant solution is injected intramuscularly into the rabbit, a lesion at the site of injection having a size of 610 cubic millimeters is produced after two days.

Example 3

A 25% solution of progesterone is prepared by dissolving 2.5 g. of progesterone in benzyl benzoate to make 10 ml. Sterilization is obtained by autoclaving the solution at 121° C. for 2 hours. When 0.25 mg. of this solution is injected into the vastus lateralis muscle of the rabbit, a lesion is produced which, after 2 days, measures 672 cubic millimeters.

When 2.5 g. of progesterone are dissolved to make 10 ml. in a mixture of 50% benzyl benzoate and 50% castor oil as the vehicle, and 0.25 ml. of this solution is injected into the rabbit muscle, a lesion size of 898 cubic millimeters is produced after two days.

Example 4

A 50% solution of hormones is prepared by dissolving 2.5 g. of progesterone and 2.5 g. of 17-hydroxyprogesterone caproate in benzyl benzoate to make 10 ml. of final product. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle and the lesion size is measured after 2 days. A lesion consisting of 572 cubic millimeters was produced. When this same hormone combination in the same proportions was dissolved in a vehicle consisting of 46% benzyl benzoate and 54% castor oil, a rabbit muscle lesion size of 1047 cubic millimeters is produced 2 days after injection of 0.25 ml. of test material.

Example 5

A 40% solution of testosterone enanthate is prepared by dissolving 4.0 g. in benzyl benzoate to make 10 ml. of final volume. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into the vastus lateralis muscle of the rabbit and the lesion size is measured after 2 days. A lesion consisting of 847 cubic millimeters is produced.

When this same quantity of hormone is dissolved in a vehicle consisting of 20% benzyl benzoate and 80% sesame oil and 0.25 ml. is injected a lesion size of 1441 cubic millimeters is produced.

Example 6

A 5% solution of Δ^1-testololactone is prepared by dissolving 50 mg./ml. in benzyl benzoate and after autoclaving to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle. After 2 days a lesion size of only 483 cubic millimeters is produced.

Example 7

15 mg. of Δ^1-testololactone is dissolved in a solution comprised of 7.5 ml. of benzyl benzoate and 2.5 ml. of castor oil. The resultant solution is sterilized, then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for 2 hours. The injectable solution may then be administered to the patient being treated.

This invention may be variously otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A parenterally administrable pharmaceutical composition comprising the acetophenonide of 16,17-dihydroxyprogesterone and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

2. A parenterally administrable pharmaceutical composition comprising testosterone palmitate and a physiologically acceptable non-toxis pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

3. A parenterally administrable pharmaceutical composition comprising testosterone enanthate and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

4. A method of administering a large single dosage of a steroid which comprises parenterally administering to the patient being treated a composition comprising a steroid selected from the group consisting of 17-hydroxyprogesterone, the caproate ester of 17-hydroxyprogesterone, testosterone, the enanthate ester of testosterone, the palmitate ester of testosterone, estradiol, progesterone, and Δ^1-testololactone, and a pharmaceutical carrier, said carrier being at least 75% by volume of benzyl benzoate.

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